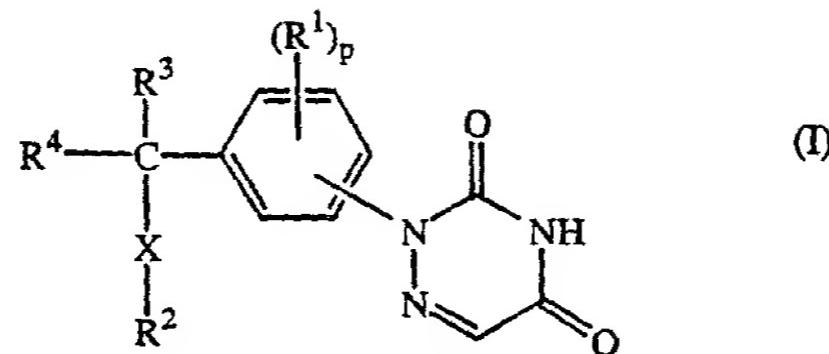


Claims

1. A compound having the formula



- a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :
- 5 p represents an integer being 0, 1, 2, 3 or 4;
- 10 X represents O, S, NR⁵ or a direct bond;
- 15 Y represents O, S, NR⁵, or S(O)₂;
- 20 each R¹ independently represents C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, NR⁷R⁸ or C₁₋₄alkyl substituted with Het³, R⁶ or NR⁷R⁸;
- 25 R² represents Het¹, C₃₋₇cycloalkyl, C₁₋₆alkyl or C₁₋₆alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy, C₁₋₆alkylsulfonyloxy, C₁₋₆alkyloxycarbonyl, C₃₋₇cycloalkyl, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR⁵, then R² may also represent aminocarbonyl, aminothiocarbonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl;
- 30 R³ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl;
- 35 R⁴ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; or
- 40 R³ and R⁴ taken together form a C₂₋₆alkanediyl;
- 45 R⁵ represents hydrogen or C₁₋₄alkyl;
- 50 each R⁶ independently represents C₁₋₆alkylsulfonyl, aminosulfonyl, mono- or di-(C₁₋₄alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl, phenylC₁₋₄alkylsulfonyl, piperazinylsulfonyl, amino-piperidinylsulfonyl, piperidinylaminosulfonyl, N-C₁₋₄alkyl-N-piperidinylaminosulfonyl or mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkylsulfonyl;
- 55 each R⁷ and each R⁸ are independently selected from hydrogen, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, arylcarbonyl, Het³carbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³, Het⁴ and R⁶;

R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, phenylcarbonyl, Het³carbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or
5 di(C₁₋₄alkyl)aminoC₁₋₄alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³, Het⁴ and R⁶;
each R¹¹ independently being selected from hydroxy, mercapto, cyano, nitro, halo,
10 trihalomethyl, C₁₋₄alkyloxy, formyl, trihaloC₁₋₄alkylsulfonyloxy, R⁶, NR⁷R⁸, C(=O)NR⁷R⁸, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, aryl, aryloxy, arylcarbonyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyloxy, phthalimide-2-yl, Het³ and C(=O)Het³;
15 R¹² and R¹³ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, phenylcarbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴ and R⁶;
20 each R¹⁴ independently represents hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl, aminocarbonylmethylene or mono- or di(C₁₋₄alkyl)aminocarbonylmethylene; aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-O-R¹⁴, R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl substituted with hydroxy, C₁₋₄alkyloxy, C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³ or NR⁹R¹⁰;
25 Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each
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independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het² and R¹¹;

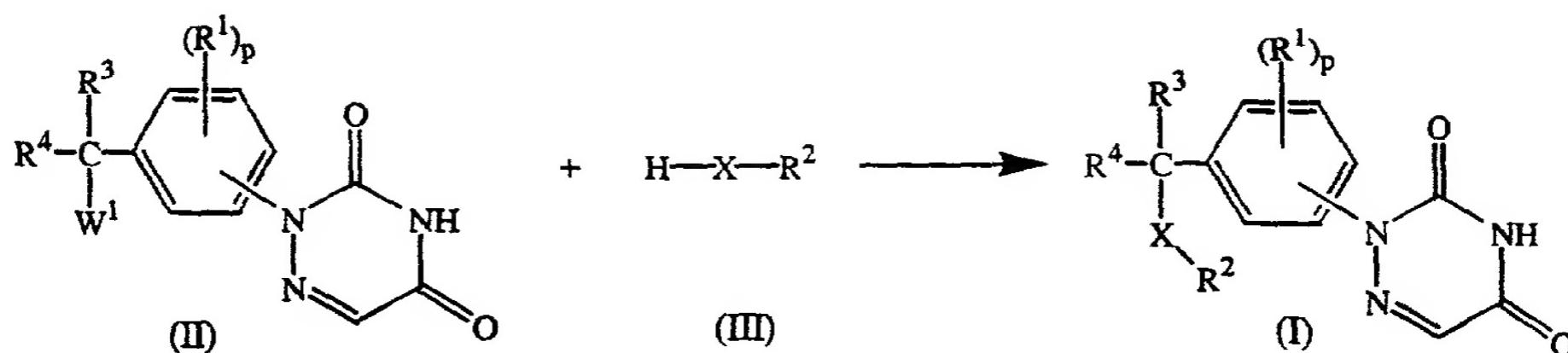
- Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het⁴, R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het⁴ and R¹¹;
- 10 Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹²R¹³, C(=O)-O-R¹⁴, R⁶ and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, phenyl, C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, R⁶ and NR¹²R¹³;
- 15 Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl.
- 20 2. A compound as claimed in claim 1 wherein each R⁷ and each R⁸ are independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, aryl-carbonyl, Het³carbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkyl-carbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³ and R⁶;
- 25 30 R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, phenylcarbonyl, Het³carbonyl,
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- C₁₋₄alkylcarbonyloxyC₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl,
C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl,
phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl,
Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-
O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³ and R⁶;
R¹¹ is being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl,
C₁₋₄alkyloxy, formyl, trihaloC₁₋₄alkylsulfonyloxy, R⁶, NR⁷R⁸, C(=O)NR⁷R⁸,
-C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, aryl, aryloxy, arylcarbonyl,
C₃₋₇cycloalkyl, C₃₋₇cycloalkyloxy, phthalimide-2-yl, Het³, Het⁴ and C(=O)Het³; and
10 Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl,
imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl,
thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl,
thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl,
pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl,
benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl,
benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]-
pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl,
quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo-[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be
20 substituted with one, or where possible, two or three substituents each
independently selected from R¹¹ and C₁₋₄alkyl optionally substituted with one or
two substituents independently selected from R¹¹.
3. A compound as claimed in claim 1 or 2 wherein the compound of formula (I)
25 contains an ester function.
4. A compound as claimed in any one of claims 1 to 3 provided that those compounds
wherein X is a direct bond, at least one of R³ and R⁴ is hydrogen, and R² is
3-pyridinyl optionally substituted in the 6 position with an optionally substituted
30 alkyl or acyl group are excluded.
5. A compound as claimed in any one of claims 1 to 4 wherein the 6-azauracil moiety
is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴
35 substituents.
6. A compound as claimed in any one of claims 1 to 5 wherein R² is a monocyclic
heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl,
furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl,

oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹.

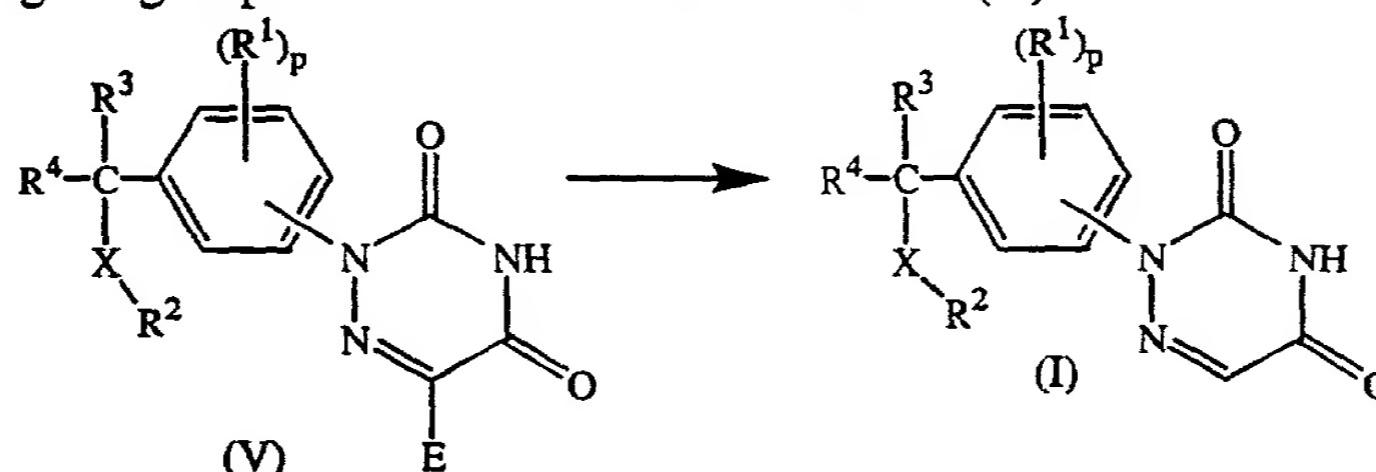
- 5 7. A compound as claimed in any one of claims 1 to 6 wherein R³ and R⁴ are both methyl and -X-R² is Het¹.
- 10 8. A compound as claimed in any one of claims 1 to 7 wherein p is 1 or 2 and each R¹ is chloro.
- 15 9. A compound as claimed in any one of claims 1 to 8 wherein R³ and R⁴ are both methyl, -X-R² is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.
- 20 10. A compound as claimed in claim 1 wherein the compound is
2-[3,5-dichloro-4-[1-methyl-1-(4-phenyl-2-thiazolyl)ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
2-[3,5-dichloro-4-[1-[4-(3-chlorophenyl)-5-methyl-2-thiazolyl]-1-methylethyl]-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
2-[3,5-dichloro-4-[1-methyl-1-(5-phenyl-1,2,4-oxadiazol-3-yl)ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
- 25 2-[3,5-dichloro-4-[1-(4,5-diphenyl-2-thiazolyl)-1-methylethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
2-[3,5-dichloro-4-[1-methyl-1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]ethyl]-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
- 30 2-[3,5-dichloro-4-[1-methyl-1-(4-methyl-5-phenyl-2-thiazolyl)ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
2-[3,5-dichloro-4-[1-methyl-1-[4-phenyl-5-(3-pyridinyl)-2-thiazolyl]ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
2-[3,5-dichloro-4-[1-methyl-1-[4-phenyl-5-(phenylmethyl)-2-thiazolyl]ethyl]-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
- 35 2-[3,5-dichloro-4-[1-methyl-1-[5-(4-pyridinyl)-1,2,4-oxadiazol-3-yl]ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;

- 2-[3,5-dichloro-4-[1-methyl-1-[4-(3-thienyl)-2-thiazolyl]ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
- 2-[3,5-dichloro-4-[1-[4-(2-furanyl)-2-thiazolyl]-1-methylethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
- 5 2-[3,5-dichloro-4-[1-methyl-1-[5-(3-pyridinyl)-1,2,4-oxadiazol-3-yl]ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
- 2-[3,5-dichloro-4-[1-methyl-1-[5-(2-methyl-3-pyridinyl)-1,2,4-oxadiazol-3-yl]ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
- 10 2-[3,5-dichloro-4-[1-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione; a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.
11. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 10.
- 15 12. A process for preparing a composition as claimed in claim 11, , wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 10.
- 20 13. A compound as claimed in any one of claims 1 to 10 for use as a medicine.
14. Use of a compound as claimed in any one of claims 1 to 10 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases.
- 25 15. A compound of formula
-
- wherein R¹, R³, R⁴ and p are as defined in claim 1.
- 30 16. A process for preparing a compound as claimed in claim 1, characterized by, a) reacting an intermediate of formula (II) wherein W¹ is a suitable leaving group with an appropriate reagent of formula (III) optionally in a reaction-inert solvent and optionally in the presence of a base at a temperature ranging between - 70°C and reflux temperature;



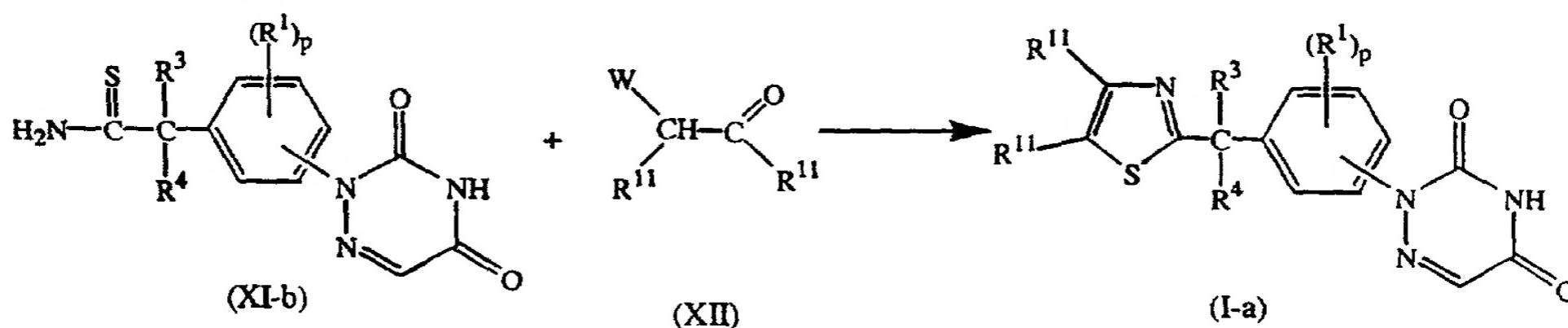
wherein R^2 , R^3 , R^4 , p and X are as defined in claim 1;

b) eliminating the group E of a triazinedione of formula (V)



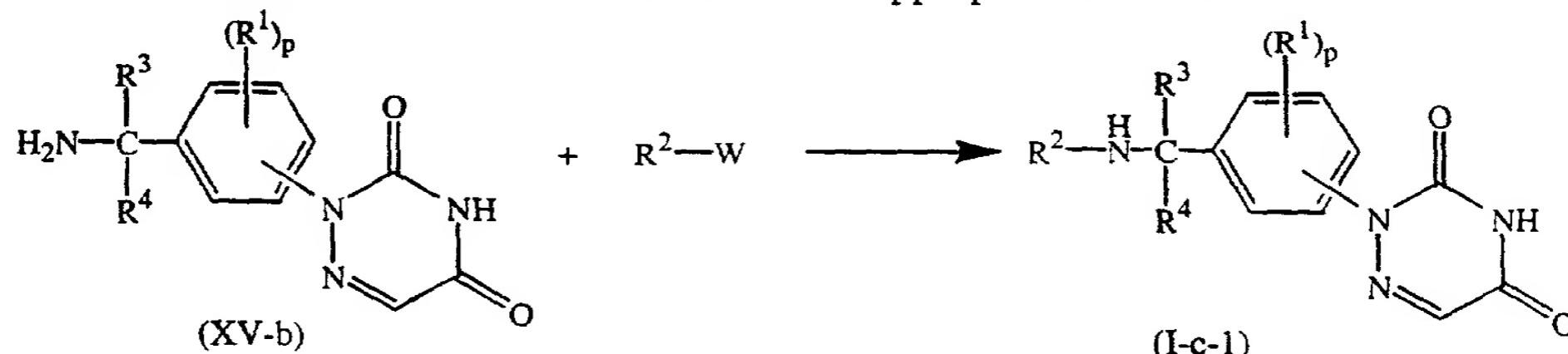
- 5 wherein E is an appropriate electron attracting group and R^1 , R^2 , R^4 , X and p are as defined in claim 1;

c) cyclizing a thioamide of formula (XI-b) with an intermediate of formula (XII) in a suitable solvent



- 10 wherein W is a suitable leaving group, and R^1 , R^3 , R^4 and p are as defined in claim 1; thus forming a compound of formula (I-a);

d) reacting an amine derivative of formula (XV-b) with an intermediate of formula R^2-W or with a functional derivative thereof in an appropriate solvent



- 15 wherein W is a suitable leaving group and R^1 , R^2 , R^3 , R^4 and p are as defined in claim 1;

- and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or
- 5 conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and also, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.
17. A process of marking a receptor comprising the steps of
- 10 a) radiolabelling a compound as defined in claim 1;
- b) administering said radiolabelled compound to biological material,
- c) detecting the emissions from the radiolabelled compound.
18. A process of imaging an organ, characterized by, administering a sufficient amount
- 15 of a radiolabelled compound of formula (I) in an appropriate composition, and detecting the emissions from the radioactive compound.